UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/041,688	01/07/2002	Yong Hua Zhu	LOMAU.143A	5449

20995 7590 04/05/2007

KNOBBE MARTENS OLSON & BEAR LLP
2040 MAIN STREET
FOURTEENTH FLOOR
IRVINE, CA 92614

EXAMINER	
GHALI, ISIS A D	
ART UNIT	PAPER NUMBER
1615	

SHORTENED STATUTORY PERIOD OF RESPONSE	NOTIFICATION DATE	DELIVERY MODE
3 MONTHS	04/05/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Notice of this Office communication was sent electronically on the above-indicated "Notification Date" and has a shortened statutory period for reply of 3 MONTHS from 04/05/2007.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

jcartee@kmob.com
eOAPilot@kmob.com

Office Action Summary	Application No.	Applicant(s)	
	10/041,688	ZHU ET AL.	
	Examiner	Art Unit	
	Isis A. Ghali	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 January 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,8,10-12,14-18,20,22-24,26-29 and 31-37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,8,10-12,14-18,20,22-24,26-29 and 31-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The receipt is acknowledged of applicants' amendment filed 01/17/2007.

Claims 7, 9, 13, 19, 25 and 30 have been canceled, claims 35-37 have been added.

Claims 1-6, 8, 10-12, 14-18, 20, 22-24, 26-29, 31-37 are pending and included in the prosecution.

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

3. Claims 1-5, 8, 10-12, 14-17, 20, 23, 24, 26-29, 31-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 96/10374 ('374) in view of US 6,2143,352 ('352).

WO '374 discloses *in situ* polymerizing (*in situ* curing) biomedical implant material and a method for repair of mammalian tissue using the same biomedical material (abstract; page 8, line 35; page 9, line 1). The material comprises cyanoacrylate adhesive, hydrophilic porosifying agent and antibiotic (page 6, lines 9, 16-17; page 7, line 1; page 8, line 23 till page 9, line 2). The hydrophilic porosifying agent includes polyethylene glycol that dissolve *in situ* as a result of exposure to an aqueous environment, e.g. body fluids are aqueous (page 4, lines 20-23). The *in situ* polymerizing implant material is introduced into the repair site (reads on wound) by variety of means and is used as a sealant in anatomic regions where it would be difficult to use a pre-cast dressing (page 12, lines 12-19). Introducing the *in situ* polymerizing implant material into the repair site reads on the step of "approximating the wound" in claim 12. Polymerization *in situ* reads on the step of curing the adhesive in claim 12. The adhesive material is a liquid as implied by its application at the site by pouring (page 12, lines 12-15).

WO '374 does not teach encapsulating the active substance and materials of the capsules as claimed in claims 1, 12, 26 and 31. WO '374 does not teach butyl and octyl cyanoacrylate as claimed in claims 2, 3, 14 and 15. WO '374 does not teach the anti-degradation agents claimed in claims 10, 11, 23 and 24.

Although the reference teaches that the porosifying agent dissolves in the aqueous environment, i.e. the body fluid, however, the reference does not teach the delivery of the substance to the tissue.

It is implied from the teaching of the reference that an active agent is delivered, such as anti-microbials including penicillin (page 12, lines 22-30). It is expected from the implanted composition that polymerizes *in situ* and comprises hydrophilic pore forming agent and active substance, to deliver the substance through the pores after the pore-forming agent dissolves.

US '352 teaches biocompatible cyanoacrylate adhesive comprises bioactive materials and other ingredients including pH modifiers are microencapsulated (col.4, lines 42-43; col.7, lines 60-65; col.8, lines 28-29, 35; col.10, lines 34-43). The microcapsules are made of bioerodible material to permits the release of the encapsulated material upon breakdown of the capsule in presence of body fluid (col.8, lines 18-26, 35). PH modifiers include materials that act as antimicrobials such as phenol compounds (col.6, lines 28-33). The reference disclosed that microencapsulation chemically protects the materials that interact with the adhesive and also provides controlled release of the bioactive agents (col.7, lines 41-43; col.10, lines 43-45). The preferred advantageous cyanoacrylates are butyl and 2-octyl cyanoacrylate

(col.3, lines 3-6; col.17, claim 13). The pH modifiers are effective to regulate the pH of an immediate environment of the in situ formed polymer to improve the usefulness of the polymers formed from the cyanoacrylate monomers and they are selected to permit the biodegradation of the in situ formed polymer to proceed more slowly than it does in physiological pH (col.2, lines 49-52; col.5, lines 38-44; col.6, lines 15-20). PH modifiers include ascorbic acid (col.6, line 49).

Accordingly, it would have been obvious to one having ordinary skill in the art at the time of the invention to provide a composition and a method for sealing wound by applying adhesive composition comprising cyanoacrylate, pore forming agent and antibiotic as disclosed by WO '374, and encapsulated the antibiotics included in the composition in a gelatin capsule as taught by US '353, motivated by the teaching of US '352 that microencapsulation chemically protects the materials that interact with the adhesive and also provides controlled release of the bioactive agents, and one having ordinary skill in the art would have selected gelatin because US '352 disclosed it as a bioerodible material that breakdown in the presence of body fluid, with reasonable expectation of having adhesive wound sealing composition and comprises cyanoacrylate, pore forming agent and antibiotic encapsulated in gelatin capsule to chemically protect the materials that interact with the adhesive and breakdown in body fluid to provide controlled release of the antibiotics, as desired by applicants.

Additionally, it would have been obvious to one having ordinary skill in the art at the time of the invention to provide a composition and a method for sealing wound by applying adhesive composition comprising cyanoacrylate, pore forming agent and

antibiotic as disclosed by WO '374, and select butyl or octyl cyanoacrylate as disclosed by US '352, motivated by the teaching of US '352 that butyl and octyl cyanoacrylates are the preferred advantageous biocompatible cyanoacrylate adhesives, with reasonable expectation of having a biocompatible adhesive wound sealing composition comprises butyl or octyl cyanoacrylate, pore forming agent and antibiotic that is safe and does not cause any harm to the wounded tissues.

Further, one having ordinary skill in the art would have been motivated to add pH modifier such as ascorbic acid (vitamin C) disclosed by US '352 to the cyanoacrylate adhesive composition disclosed by WO '374, motivated by the teaching of US '352 that pH modifiers are effective to regulate the pH of an immediate environment of the in situ formed polymer to improve the usefulness of the polymers formed from the cyanoacrylate monomers and they are selected to permit the biodegradation of the in situ formed polymer to proceed more slowly than it does in physiological pH, with reasonable expectation of having adhesive wound sealing composition comprises butyl or octyl cyanoacrylate, pore forming agent, encapsulated antibiotic, and pH modifier such as ascorbic acid wherein the composition has delayed biodegradation of the in situ formed polymer and improved usefulness of the in situ formed polymer, as desired by applicants.

The combined teachings of the references do not teach specific antibiotics as claimed in claims 27-29 and 32 and 34. In any event, applicants failed to show superior and unexpected results that are achieved from using those specific antibiotics, and they do not impart patentability to the claims, absent evidence to the contrary.

Response to Arguments

4. Applicant's arguments filed 01/17/2007 have been fully considered but they are not persuasive. The main gist of applicants argument against this rejection is WO '374 does not teach encapsulation of active substance and US '352 does not teach protective shell preventing premature polymerization of the adhesive by blocking direct contact between therapeutic agent and the cyanoacrylate adhesive, therefore, no prima facie case of obviousness has been established because the references do not disclose the problem of premature polymerization.

In response to this argument, applicants' attention is directed to the scope of the present claims that are drawn to adhesive composition and method of its use, and all the element of the claimed composition and method of its use are disclosed by the combined teaching of the references. The intended use of the capsule as a protective shell to prevent polymerization of cyanoacrylate is obvious and is implied by the teaching of US '352. In considering the disclosure of the reference, it is proper to take into account not only the specific teachings of the reference but also the inferences which one skilled in the art would reasonably be expected to draw therefrom. *In re Preda*, 401 F.2d 825, 826, 159 USPQ 342, 344 (CCPA 1968). The rational to modify or to combine the prior art does not have to be expressly stated in the prior art; the rational may be expressly or impliedly contained in the prior art or it may be reasoned from knowledge generally available to one of ordinary skill in the art. The reason or motivation to modify the reference may often suggest what the inventor has done, but

for a different purpose or to solve different problem. It is not necessary that the prior art suggest the combination or modification to achieve the same advantage or result discovered by applicant. *In re Linter*, 458 F.2d 1013, 173 USPQ 560 (CCPA 1972). WO '374 teaches cyanoacrylate composition comprising defect forming agent and active agent, and US '352 teaches cyanoacrylate composition comprising active agents microencapsulated, col.10, lines 42-45. Further, US '352 recognized encapsulation of materials incorporated in the cyanoacrylate adhesive chemical protection of the composition. Cyanoacrylate is self-curing adhesive and known to polymerize in contacting some antimicrobial agents, see US 6,086,906 that address such a problem, and one having ordinary skill in the art would appreciate that encapsulation of active agents in cyanoacrylate composition will protect the cyanoacrylate from polymerization. Accordingly, it would have been obvious to one having ordinary skill in the art at the time of the invention to provide a composition and a method for sealing wound by applying adhesive composition comprising cyanoacrylate, pore forming agent and antibiotic as disclosed by WO '374, and encapsulated the antibiotics included in the composition in a gelatin capsule as taught by US '353, motivated by the teaching of US '352 that microencapsulation chemically protects the materials that interact with the adhesive and also provides controlled release of the bioactive agents, and one having ordinary skill in the art would have selected gelatin because US '352 disclosed it as a bioerodible material that breakdown in the presence of body fluid, with reasonable expectation of having adhesive wound sealing composition and comprises cyanoacrylate, pore forming agent and antibiotic encapsulated in gelatin capsule to

chemically protect the materials that interact with the adhesive and breakdown in body fluid to provide controlled release of the antibiotics, as desired by applicants.

It is well established that the claims are given the broadest interpretation during examination. A conclusion of obviousness under 35 U.S.C. 103 (a) does not require absolute predictability, only a reasonable expectation of success; and references are evaluated by what they suggest to one versed in the art, rather than by their specific disclosure. *In re Bozek*, 163 USPQ 545 (CCPA 1969).

In the light of the foregoing discussion, the Examiner's ultimate legal conclusion is that the subject matter defined by the claims would have been *prima facie* obvious within the meaning of 35 U.S.C. 103 (a).

5. Claim 22 is rejected under 35 U.S.C. 103(a) as being unpatentable over WO '374 in view of US '352 and further in view of WO 96/00760 ('760).

The teachings of WO '374 in view of US '352 are discussed above.

However, WO '374 in view of US '352 do not teach the wound as a lacerated wound as in claim 22.

WO '760 teaches a biocompatible composition comprising pH modifier and butyl and octyl cyanoacrylate monomer wherein the composition is useful as biomedical and surgical adhesive and sealant that finds uses in repairing traumatically lacerated tissues, as claimed by present claim 22 (abstract; page 4, lines 6-12; page 5, line 17). In presence of blood, the composition has adequate flexibility and strength to withstand

normal movement of the tissue and a bond strength that is maintained as natural tissue healing proceeds (page 6, lines 15-19; page 18, lines 23-32).

Accordingly, it would have been obvious to one having ordinary skill in the art at the time of the invention to provide composition and method for sealing the wound using adhesive composition comprising octyl or butyl cyanoacrylate, pore forming agent and encapsulated antibiotic as disclosed by WO '374 in view of US '352 and use the composition to treat lacerated wounds as disclosed by WO '760 motivated by the teaching of WO '760 that the cyanoacrylate composition finds uses in traumatically lacerated tissues because it has adequate flexibility and strength in presence of blood to withstand normal movement of the tissue and has a bond strength that is maintained as natural tissue healing proceeds, with reasonable expectation of having strong flexible wound sealant that comprises butyl or octyl cyanoacrylate, pore forming agent, encapsulated antibiotic useful for traumatically lacerated wounds as it can withstand normal movement of the tissues and has a bond strength that is maintained as natural tissue healing proceeds.

Response to Arguments

6. Applicant's arguments filed 01/17/2007 have been fully considered but they are not persuasive. Applicants argue that WO '760 does not include any additional disclosure overcoming the deficiencies of WO '374 and US '352 that do not teach all the limitations of claims 1 and 12.

In response to his argument, the examiner hereby repeats the response regarding WO '374 combined with US '352, and further add that WO '760 is relied upon for the teaching of the species of the cyanoacrylate and to show them as known in the wound dressing art, and also for the teaching of anti-degradation agents incorporated in wound dressings to treat lacerated wounds. It has been held that a prior art reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the applicant was concerned, in order to be relied upon as a basis for rejection of the claimed invention. See In re Oetiker, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992). In this case, all the cited references are in the field of applicants' endeavor and concerned to the same problem as applicants, which problem is wound dressing comprising octyl and butyl cyanoacrylate and anti-degradation agents.

7. Claims 6 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO '374 in view US '352 and further in view of WO 99/20685 ('685).

The teachings of WO '374 in view of US '352 are discussed above.

However, the combined teachings of WO '374 in view of US '352 does not teach the molecular weight of the polyethylene glycol as claimed in claims 6 and 18.

WO '685 teaches a formulation that forms a film comprising water soluble pore forming agent such as polyethylene glycol that leaches out through the film *in situ* and creates a perforations that regulate the release rate of active agents (page 7, lines 10-16). The preferable molecular weight of the polyethylene glycol that is able to create

adequate pore size for controlling the release of the active agents is from 540 to 8000, i.e. encompasses the molecular weight claimed by applicants in claims 6 and 18 (page 9, lines 23-28; page 10, lines 1-2).

Accordingly, it would have been obvious to one having ordinary skill in the art at the time of the invention to provide composition and method for sealing the wound wherein the composition comprises butyl or octyl cyanoacrylate, polyethylene glycol as pore forming agent and encapsulated antibiotics as disclosed by WO '374 in view of US '193 and select the molecular weight of the polyethylene glycol between 540 and 8000 as taught by WO '685 because this range of molecular weight is preferred because of the ability of polyethylene glycol having such molecular weight to create adequate pore size for controlling the release of the active agents, with reasonable expectation of success of having wound sealant composition comprising butyl or octyl cyanoacrylate, polyethylene glycol with molecular weight ranging from 540 to 8000 as pore forming agent and encapsulated antibiotics wherein the polyethylene glycol creates pores of adequate sizes for controlling the release of antibiotics to the treated wound.

Response to Arguments

8. Applicant's arguments filed 01/17/2007 have been fully considered but they are not persuasive. Applicants argue that WO '760 does not include any additional disclosure overcoming the deficiencies of WO '374 and US '352 that do not teach all the limitations of claims 1 and 12.

In response to his argument, the examiner hereby repeats the response regarding WO '374 combined with US '352, and further add that WO '685 is relied upon for the solely teaching the specific molecular weight of PEG and to show them as known in the wound dressing art as pore forming agents. It has been held that a prior art reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the applicant was concerned, in order to be relied upon as a basis for rejection of the claimed invention. See In re Oetiker, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992). In this case, all the cited references are in the field of applicants' endeavor and concerned to the same problem as applicants, which problem is wound dressing comprising cyanoacrylate and PEG of specific molecular weight as a pore-forming agent.

9. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. US 6,086,906 addressed the problem of premature polymerization of cyanoacrylate when incorporated with some antimicrobial agents, and in effort to overcome the problem, the reference used some specific antimicrobial agents, see col.1, lines 10-12, 50-60; col.8, lines 26-35.

Conclusion

10. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Isis A. Ghali whose telephone number is (571) 272-0595. The examiner can normally be reached on Monday-Thursday, 7:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward can be reached on (571) 272-8373. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should

you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Isis A Ghali
Primary Examiner
Art Unit 1615

IG

ISIS GHALI
PRIMARY EXAMINER